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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/580,380	05/26/2000	Bradford W. Gibson	UCSFP001/1584.002	1111

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Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	9

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/580,380	GIBSON ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *7,15-19 and 26-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-14,20-25 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-74* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traversal of Group I, claims 1-26, 73, and 74, mass spectrometer and proteins, in Paper No. 8, filed June 02, 2003, is acknowledged.

2. The traversal is on the ground(s) that it would not be unduly burdensome to perform a search on claims Groups I, III, and IV together. This is not found persuasive because these distinct methods and system groups are directed to different subject matters and active steps for achieving their respective intended goals. These methods and systems have distinct goals as requiring distinct and different functions and results thereof without overlapping search due to different subject matter. This lack of overlapping searches documents the undue search burden if they were search together.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claims 27-72 have been withdrawn due to being directed to non-elected subject matter.

5. Further, claims 7, 15-19, 26, and 73 have been withdrawn due to being directed to subject matter other than the elected species, mass spectrometer and proteins. It is noted that claims 15 and 26 employ a combination of methods including mass spectrometric analysis. These claims have been withdrawn due to having limitations that are beyond the elected specie of mass spectrometer analysis and protein.

6. Claims 1-6, 8-14, 20-25, and 74 are examined on the merits.

OBJECTIONS

7. Claim 8, line 6, 12, line 2, and 20, lines 1 and 2, are objected to because of the following informalities: These claims contain terms or phrases that are underlined. Appropriate correction is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-6 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Specific to claim 1, line 4, the term "smaller" causes the claim to be vague and indefinite because it is unclear what criteria are being used to determine that one molecular fragment is "smaller" than another. Applicants do not provide a reference point to which a comparison can be made to determine that one molecular fragment is "smaller" than another. Is a molecular fragment "smaller" due to the three-dimensional volume? Further, is a molecular fragment "smaller" due to having less number of residues compared to the macromolecule that was fragmented or other fragments? Clarification of the metes and bounds is required. Claims 2-6, and 13 are rejected for being dependent from claim 1.

11. Specific to claim 5, line 2, the phrase "best fit" causes the claim to be vague and indefinite because it is unclear what criteria are being used to determine that a structure "best fit" the distance constraints (numerical distance values or actual distance occupied by the size of the modeled molecules). Clarification of the metes and bounds is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making

> and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-6, 8-14, 20-25, and 74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using equation of claim 24 to determine the tertiary structure (3D) of a macromolecule such as a protein by cross-linking the said protein for analysis by mass spectroscopy, does not reasonably provide enablement for the determination of the tertiary structure (3D) of a macromolecule such as a protein by any other methods (X-ray crystallography etc.) or mathematical equations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

14. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

15. It is acknowledged that Applicants provide enablement disclosure for determining tertiary structure (3D) of a macromolecule such as a protein by cross-linking the said protein for analysis

by mass spectroscopy (Examples 1-3) and generating a hypothetical structure according to the equation of Page 36.

16. It is noted that Applicants disclose that determining tertiary structure (3D) of a macromolecule such a protein can be achieved via X-ray crystallography and NMR and such techniques are unpredictable due to the difficulty of the said method (page 12, lines 13-27). Further, it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002).

17. Further, Applicants do not provide to one of skill in the art to use any other equations to generate the hypothetical structure of the claimed invention.

18. Accordingly, it would be unpredictable for one of skill in the art to use any other techniques such X-ray crystallization or NMR beyond the method, 3D structure determination via cross-linking protein for analysis by mass spectroscopy, disclosed in the instant specification. In light of the difficulty of the art of determining 3D structure (X-ray crystallization etc), it is, therefore, unreasonable to expect one of skill in the art to use the information disclosed for one specific method, determining tertiary structure (3D) of a macromolecule such as a protein by

cross-linking protein for analysis by mass spectroscopy, to practice the invention with any other method (X-ray crystallization etc) without undue experimentation.

19. In light of the lack of guidance for using any other equation for generating the hypothetical structure of the claimed invention, it is, therefore, unreasonable to expect one of skill in the art to use the information disclosed for one specific equation to determine the tertiary structure (3D) of a macromolecule such as protein by cross-linking protein for analysis by mass spectroscopy to practice the invention with any other equations without undue experimentation.

CLAIM REJECTIONS - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

21. A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1-6, 8, 14, 20-23, 25, and 74 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Lacroix et al. (1997).

23. Lacroix et al. discloses a method for three-dimensional modeling based on chemical cross-linking and homology modeling (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling §) wherein the EDC cross-linked protein isolated and fragmented by proteolysis (Abstract et al.). The fragmented peptides are identified by mass spectrometry (page 6272, Mass Spectrometry Analysis §). The peptides are constrained as to the distance between Gly280 – Met351 from the N-terminus (Figure 5) and the sequence are determined by Edman degradation (Figure 7), as in instant claims 1-3, 6, and 8.

24. Scoring values are assigned to fragments having specific distance (Table 1), as in instant claims 4, 5, 20 and 21.

25. Crossed linked fragment are enriched by fractionation of the reaction mixtures (Figure 1), as in instant claim 14.

26. The virtual library of proteolyzed products is represented by Table 1, which consists of average mass data (Table 1 and page 6274, column 1, lines 18-24), as in instant claim 22.

27. The hypothetical structures of the peptides with the predicted protein folds are illustrated in Figures 9-11. Further, Lacroix et al. discloses the homology modeling is similar to that of Rossi et al. 1995 (page 6272, column 1, Computer-Assisted Three-dimensional Homology Modeling §). Rossi et al. discloses "threading" wherein a set of homologous three-dimensional structures is used as a reference template, sequence of proteins are aligned and the candidate structure is identified by comparing the said structure to the reference set (Rossi et al., page 7313, Computer-Assisted Three-dimensional Homology Modeling §, columns 1-2), as in instant claims 23, 25, and 74.

CLAIM REJECTIONS - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

29. (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to

which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31.

32. Claims 1-6, 8-14, 20-23, 25, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lacroix et al. (1997) taken with Mitra et al. (1979).

33. Lacroix et al. (1997) discloses the limitations of claims 1-6, 8, 14, 20-22, 23, 25, and 74 as discussed above. However, Lacroix et al. does not disclose the specific limitations of claims 9-13.

34. Mitra et al. discloses the general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) such as bifunctional reagents (page 3106, column 2, Discussion §, lines 12-13) which reaction with amines (page 3100, column 1, lines 64-65) as in instant claims 9 and 10.

35. Two reagents are synthesized wherein one reactions with a nuclease between lysine residues 7 and 37 and the other at 31 and 41 (Abstract etc.), as in instant claims 11 and 12.

36. The first cross-link is introduced to allow a new conformation for the second link to take place (page 3108, column 1, lines 9-12), as in instant claim 13. It is noted that the first cross-link reaction is optimized to introduce one cross-linker per molecule before the second cross-linker can be introduced.

37. Mitra et al. discloses reagents such as cross-linking reagents have wide application to the studies protein structure and the said agents are important tools for biochemist and molecular biologists for protein structure determination (page 3110, column 1, lines 22-30). Therefore, Mitra et al. suggests that cross-linking reagents are applicable and important tools to determining the tertiary structure of proteins such as the Clr serine protease of Lacroix et al.

38. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the concept emphasized by Mitra et al. for general chemical techniques for establishing the tertiary structures of proteins based on cross-linking reagents (page 3097, Introduction §, lines 1-4) to use the method Lacroix et al. for determining the tertiary structure of a protein with the cross-linking reagents of Mitra et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for three-dimensional modeling based on chemical cross-linking and homology modeling as taught by Lacroix et al. and use the said method with the cross-linker reagents as taught Mitra et al.

CONCLUSION

39. NO CLAIM IS ALLOWED.

40. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157

OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

42. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

43. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
8/19/03

ARDIN H. MARSCHEL
PRIMARY EXAMINER